REMARKS

STATUS OF THE CLAIMS

Claims 1-14 and 21-25 were pending in this application. Claims 21-25 have been cancelled without prejudice. Following entry of the amendments, claims 1-14 will be pending and at issue.

RESTRICTION REQUIREMENT

In the Office Action of 09/25/03, the Examiner stated that the Response filed 07/11/03 was not fully responsive to the prior Office Action "because of the following omissions or matters: applicant has reintroduced subject matter that was subject to a restriction and an election is required."

In the 11/25/03 Response, Applicant elected without traverse SEQ ID NO:80 of claim 3. As described in the Office Action of 09/25/03 and reiterated during the Examiner Interview on October 30, 2003, the restriction of claim 3 is subject to the non-allowance of linking claim 1. Upon the allowance of linking claim 1, the restriction requirement as to the linked inventions shall be withdrawn and any claims depending from or otherwise including all the limitations of the allowable linking claims will be entitled to examination in the instant application.

IDS

Applicant notes with appreciation the Examiner's thorough consideration of the references cited in the IDS (Form 1449) submitted on August 1, 2002.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

In the Office Action of 09/25/03, claims 15-20 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Without agreeing with the Examiner's rejection but to expedite prosecution of this application, Applicant has cancelled claims 15-20, rendering the rejection moot.

REJECTIONS UNDER 35 U.S.C. § 103

In the Office Action of 09/25/03, claims 1, 2, and 4-15 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Andres [PNAS Vol. 96:9873-9878] and Bennett et al [US 5,988,148], Baracchini et al [US 5,801,154], Weintraub [Scientific American, January 1990, pages 40-46], and GenBank AI922671 (SEQ ID NO:11). Applicant has cancelled herein claim 15, rendering moot this rejection of claim 15. Applicant respectfully traverses this ground of rejection with respect to claims 1, 2, and 4-14.

The Examiner stated that "At page 40 of the specification it is admitted that the antisense of the invention were designed based on the published sequence of CoREST referenced as AI922671 (SEQ ID NO:11)." First, Applicant respectfully points out that page 40 of the specification does not discuss target sequences; Applicant assumes the Examiner meant to reference page 80 of the specification. Second, GenBank AI922671 is not SEQ ID NO:11, but rather the complement of SEQ ID NO:12 (see page 80). GenBank AI922671 (complement of SEQ ID NO:12) is a cDNA sequence, while SEQ ID NO:11 is a human genomic CoREST sequence. As the instant claims are drawn to antisense compounds targeted to SEQ ID NO:11, the use of GenBank AI922671 (SEQ ID NO:12) as prior art disclosing the sequence of the target is improper.

Applicant requests withdrawal of this rejection of the claims based on the above error. However, in the interest of furthering prosecution, Applicant also responds to the Examiner's rejections as follows.

The claimed invention is a compound targeted to a nucleic acid encoding CoREST (SEQ ID NO:11) wherein said compound hybridizes to and inhibits expression of the nucleic acid. (Applicant respectfully points out that amended claims 1 and 11 include the language "SEQ ID NO:11" and not "SEQ ID NO:3" as described by the Examiner). The invention also includes dependent claims where the compound is an antisense oligonucleotide which have various recited modifications and where the antisense compounds are included in various carriers.

The Examiner has presented the combination of Andres (teaching that CoREST mediates repression of the Type I sodium channel promoter in neuronal cells) with two other pieces of art that teach antisense inhibitory molecules of specific, non-CoREST targets: Bennett et al (teaching antisense modulation of microtubule–associated protein 4) and Baracchini et al (teaching antisense modulation of multidrug resistance-associated protein, or MRP), together with Weintraub's review of antisense technology, combined with the published sequence of CoREST referenced as GenBank AI922671. The Examiner has failed to make a prima facie case of obviousness for the following reasons:

I. the combination of art cited by the Examiner is based on improper hindsight and does not provide a teaching or suggestion to combine the teachings;

II. the combination of art cited by the Examiner at best provides a generalized incentive insufficient to render obvious the claimed invention; and

III. one of skill in the art would have had no expectation of success when combining the elements taught by the cited combination of art.

I. The combination of Andres with Bennett et al, Baracchini et al, Weintraub, and GenBank AI922671 is based on improper hindsight.

To render a claim unpatentable under 35 U.S.C. § 103, there must be some suggestion or motivation, either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. The teaching or suggestion to make the claimed combination must be found in the prior art, not in applicant's disclosure. *In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP §§ 2143, 2143.01. The Examiner's rejection is improper because there is no motivation (outside Applicant's own disclosure) to modify or combine the teachings of Andres with Bennett et al, Baracchini et al, Weintraub, and GenBank AI922671 to obtain the specific compounds of the claims. Instead, the combination is impermissible hindsight based on Applicant's own disclosure.

As the Examiner admits, Andres does not specifically teach the use of antisense oligonucleotides to inhibit CoREST. Neither Bennett et al, Baracchini et al, nor Weintraub remedy this deficiency. There is nothing in the Bennett et al or Baracchini et al to suggest that an ordinarily skilled artisan would read the disclosures as a generic teaching to design antisense oligonucleotides targeted to any and all disease-associated gene targets. Rather, Bennett et al and Baracchini et al teach antisense oligonucleotides to specific targets, e.g., microtubule–associated protein 4 and multidrug resistance-associated protein (MRP), respectively.

Applicant submits that the teachings of Baracchini et al identified by the Examiner would be interpreted by one of ordinary skill in the art as pertaining specifically to the MRP gene target. On page 8 of the Office Action, the Examiner cites Baracchini et al as follows:

> Baracchini et al have taught, at column 6 for example, that antisense oligonucleotides can be used for research purposes and have also taught, at column 6, that antisense oligonucleotides can be modified in their sugars, backbone linkages and nucleobases and that such modifications are desirable in antisense since these modifications have desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid targets and increases stability in the presence of nucleases. Baracchini et al provide specific examples of such modifications at columns 6-8 and in Example 1, for example. These specific examples taught by Baracchini et al include phosphorothioate linkages, 2'-O-methoxyethyl sugars, 5-methylcytosine and chimeric oligonucleotides, for example. Tables 1-4 show the successful design and use of modified oligonucleotides in cells in culture, for example. Table I therefore reflects the successful practice of general antisense design taught at columns 8-10, for example. At column 4 it has been taught various carriers for antisense delivery. It has been taught at column 8 that antisense are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length, for example.

Applicant respectfully points out that the Examiner has misstated the passages from Baracchini et al. Baracchini et al does not provide a generic teaching of how to design and make antisense oligonucleotides, but rather a specific teaching of antisense oligonucleotides targeted to MRP only. For example, this is demonstrated by the following passages from column 6-8:

The oligonucleotides of this invention may also be used for research purposes. Thus, the specific hybridization exhibited by the oligonucleotides may be used for assays, purifications, cellular product preparations and in other methodologies, which would be appreciated by persons of ordinary skill in the art.

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The present invention employs oligonucleotides for use in antisense inhibition of the function of RNA and DNA encoding multidrug resistance-associated protein (MRP).

Similarly, each of the antisense oligonucleotides listed in Tables 1-4 is directed to the MRP gene, as evidenced by the tables' titles. Thus, the references in Baracchini et al cited by the Examiner are all tied to the MRP gene, the expression of which Baracchini et al's invention seeks to inhibit.

In a similar manner, the references in Bennett et al cited by the Examiner are all tied to the microtubule–associated protein 4 gene, the expression of which Bennett et al's invention seeks to inhibit. There is nothing to suggest that one of ordinary skill reading Baracchini et al and Bennett et al would interpret their teachings in the expansive manner suggested by the Examiner and so combine them with those of Andres.

Weintraub merely teaches use of antisense oligonucleotides to elicit information about gene function. Weintraub does not provide any specific teachings of how to design and make antisense oligonucleotides. Further, Weintraub does not provide any motivation to combine the specific target of CoREST and the gene sequence of CoREST with MRP-specific teachings of Baracchini et al and the microtubule–associated protein 4 specific teachings of Bennett et al. Instead, the combination is motivated by Applicant's own disclosure and so cannot be relied upon to make out a prima facie case of obviousness. Accordingly, the rejected claims are patentable over the cited art.

II. The combination of art at best provides a generalized incentive insufficient to render obvious the claimed species.

The combination of art cited by the Examiner also fails to render obvious the rejected claims because the references at best contain a generalized incentive to make antisense molecules against CoREST, based on the discovery and characterization of the CoREST protein reported in the Andres reference and, e.g., the sequence disclosed in GenBank AI922671. The combination therefore fails to make out a prima facie case of obviousness because "a general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel* 51 F.3d at 1559, 34 USPQ2d at 1216. The combination of art at best provides only a generalized incentive to make antisense against CoREST, and no teaching or suggestion to make the specific antisense nucleic acids claimed. Assuming *arguendo* that Baracchini et al and Bennett et al could fairly be read in the expansive manner suggested by the Examiner and so properly be combined with Andres, the combination of art cited by the Examiner at best provides a general incentive to design antisense nucleic acids to any given target. The combination fails to teach or suggest the specific mRNA or cDNA polynucleotide sequences necessary to select the specific antisense nucleic acid molecules claimed and therefore fails to teach or suggest the particular antisense nucleic acids claimed.

Applicant notes that the number of potential antisense oligonucleotides targeted to CoREST encompasses a vast number of possibilities. As the Federal Circuit held in *In re Baird*, disclosure of a broad genus does not necessarily render obvious each compound within its scope. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). Thus, even though the prior art included a polynucleotide sequence encoding CoREST from which potential antisense molecules could be designed, the specific antisense molecules instantly claimed (e.g., those that specifically hybridize and inhibit expression) still would not be obvious given the failure of the prior art to teach or suggest these specific molecules.

III. Inhibitory antisense oligonucleotide design at the time of the invention was not sufficiently predictable from gene to gene to provide a generic reasonable expectation of success

Even if Applicant were to assume *arguendo* that the Examiner properly had identified a motivation to combine the cited references, the 35 U.S.C. § 103 rejection still would be improper. Modifying or combining art to make out a prima facie case of obviousness also requires that the prior art provide an ordinarily skilled artisan working at the time of the invention with a reasonable expectation of success in making the claimed invention. MPEP § 2143.02.

Applicant submits that the cited references fail to provide a reasonable expectation of success because the cited references, alone or in combination, fail to provide direction as to which of many possible choices of CoREST antisense molecules was likely to be successful. As such, the cited combination at best makes the claimed invention "obvious to try." It does not render it obvious. *See In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

Given the completely unrelated sequences of nucleic acids encoding CoREST on the one hand and those encoding MRP and microtubule–associated protein 4 on the other, there is nothing in the approaches to designing antisense oligonucleotides used by Baracchini et al and Bennett et al, nor in the sequences of the specific antisense molecules found by Baracchini et al and Bennett et al, nor the general teaching provided by Weintraub, that could provide direction as to the successful selection of antisense molecules that would specifically hybridize with and inhibit expression of a CoREST nucleic acid molecule. Thus, the cited combination fails to make out a prima facie case of obviousness.

CONCLUSION

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicant's representative at (415) 875-2316.

Respectfully submitted,
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